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Review Article

Transthyretin cardiac amyloidosis in aortic stenosis: Prevalence, diagnostic challenges, and clinical implications

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ABSTRACT

Transthyretin cardiac amyloidosis (ATTR-CA) is a challenging and underdiagnosed cause of heart failure. Advances in cardiac imaging have enabled noninvasive diagnosis of ATTR-CA, causing the recent upsurge in disease awareness and detection. ATTR-CA has been increasingly recognized in patients with degenerative aortic stenosis (AS). With the growing number of elderly patients undergoing aortic valve intervention, the identification of ATTR-CA in this group of patients is of high clinical importance. Timely and correct diagnosis is essential for amyloid-directed therapies, as well as deciding on the AS treatment strategy. This review provides a comprehensive overview of the recent studies investigating coexistence of these two entities. We present the data on the prevalence of ATTR-CA in AS and their prognostic associations. As the diagnosis of ATTR-CA may be challenging, special attention is paid to the diagnostic utility of different imaging modalities, namely, echocardiography, cardiovascular magnetic resonance, nuclear imaging, and distinctive imaging features, in patients with dual pathology. We also present a flowchart summarizing integrated imaging in patients with suspected ATTR-CA.

1. Introduction

Transthyretin cardiac amyloidosis (ATTR-CA) is described as a progressive infiltrative cardiomyopathy with ventricular wall thickening and, predominantly, diastolic heart failure.[1] ATTR-CA can be either hereditary, resulting from >120 mutations in the transport protein transthyretin, or acquired, wild-type ATTR-CA.[2,3] Until recently, ATTR-CA was considered a rare type of infiltrative cardiomyopathy, and traditional gold standard for diagnosis was positive endomyocardial biopsy in the context of characteristic clinical and imaging features. Advances in diagnostic imaging, including contrast-enhanced cardiovascular magnetic resonance (CMR) with T1 mapping.[4] and nuclear imaging with technetium-labeled bone-seeking tracers,[5,6] permit noninvasive, non-histological diagnosis of ATTR-CA that substantially increased disease awareness and recognition in the last decade.[7] Degenerative aortic stenosis (AS) is the most common valvular heart disease in developed countries.[8] Excessive remodeling of the left ventricular (LV) myocardium and restrictive physiology with preserved LV ejection fraction are both features of ATTR-CA and AS.[3,9] The prevalence of both ATTR-CA and AS increases with age, and a growing number of studies have investigated their coexistence.[10–16] As both diseases share similar clinical and

Abbreviations: AS, aortic stenosis; ATTR-CA, Transthyretin cardiac amyloidosis; CMR, cardiovascular magnetic resonance; ECG, electrocardiography; ECV, extracellular volume fraction; LGE, late gadolinium enhancement; LV, left ventricular; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; Tc-99m-DPD, Technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid; Tc-99m-HMDP, Technetium-99m-hydroxymethylene diphosphonate; Tc-99m-PYP, Technetium-99m-pyrophosphate.

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echocardiographic characteristics, recognition of superimposed ATTR-CA in patients with AS can be very challenging. However, accurate diagnosis is critical for the management of both pathologies, guiding amyloid-directed therapies and deciding on the AS treatment strategy. In this review, we aimed to summarize the available evidence on prevalence, diagnostic implications, and prognostic associations of ATTR-CA in patients with AS.

2. Prevalence of ATTR-CA in aortic stenosis

Data from postmortem studies in unselected subjects indicate a prevalence of cardiac amyloidosis of 22% to 25% in subjects older than 80 years of age.[17] In an autopsy series of patients who had undergone transcatheter aortic valve replacement (TAVR), varying degrees of ventricular myocardium amyloid infiltration was found in approximately one-third of cases.[18] In a recent series, the proportion of patients with AS identified with ATTR-CA varied greatly and was between 4% and 16%.[10,14,15,16] The large variability in the prevalence of ATTR-CA in patients with AS could be explained by different study inclusion criteria and diverse study populations investigated (Table 1). The higher prevalence of ATTR-CA was found in TAVR cohorts. Scully et al[16] reported 13.9% prevalence of ATTR-CA in patients with severe AS referred for TAVR. In a study by Castano et al,[15] occult ATTR-CA was identified in 16% of patients after TAVR. The lower prevalence of ATTR-CA was described in a cohort of patients with severe AS undergoing surgical AVR (SAVR). Amyloid deposition was identified in endomyocardial biopsies of 6 out of 146 (4%) patients at the time of SAVR.[10] The prevalence increased to 5.6% if only patients with calcific AS >65 years of age were considered. On average, patients in that study were younger and had preserved LV ejection fraction, representing a lower risk population and explaining lower prevalence of ATTR-CA. In a retrospective study by Cavalcante et al,[14] among 113 patients with severe and moderate AS, 9 had cardiac amyloidosis confirmed by CMR with Late gadolinium enhancement (LGE). It appears that approximately 1 in 7 patients currently undergoing TAVR have occult cardiac amyloidosis—a higher prevalence than that in surgical AVR cohorts. Furthermore, ATTR-CA typically affects males more than females, and the prevalence increases progressively with age. It has important clinical implications, as with aging population, the number of patients with coexistent ATTR-CA and severe AS will likely increase.

3. Diagnosing ATTR-CA in aortic stenosis

Recognition of ATTR-CA is complex owing to variability in disease clinical presentation, absence of disease specific symptoms, and ambiguous findings using common diagnostic tools. Diagnosis of ATTR-CA in AS is even more difficult, as their clinical and imaging features can overlap. Comorbidities such as coronary heart disease and hypertension frequently present in the older population, which creates a diverse clinical picture and adds to diagnostic challenges.

3.1. Electrocardiography

Patients with ATTR-CA rarely have normal electrocardiography (ECG). The most commonly observed electrocardiographic abnormality is a pseudoinfarct pattern (mainly in anterior leads), observed in approximately 60% of patients with ATTR-CA.[19–21] The association between low voltage and cardiac amyloidosis has long been considered pathognomonic; however, the prevalence in a contemporary series of ATTR-CA was as low as 20% to 30%.[19,21,22] On the contrary, up to a fifth (7-10%) of patients with ATTR-CA may show LV hypertrophy on ECG.[19,20] Direct involvement of the sinoatrial node, atrioventricular node and bundle branches can manifest as various degrees of conduction abnormalities.[19,23] As myocardial amyloid deposition is a continuum from minimal to transmural, all the above-mentioned ECG abnormalities tend to become more frequent with increasing disease severity. In a cohort of 425 patients with ATTR-CA, presence of low ECG voltage, pathologic Q waves and duration of PR, QRS, and QT intervals progressively increased with increasing thickness of interventricular septum and were most common in patients with the thickest hearts.[22] Patients with concomitant ATTR-CA and AS tend to exhibit

Table 1
Studies investigating ATTR cardiac amyloidosis in aortic stenosis

First author, study year (Ref No.)	Study design	No. of patients	Patients ATTR(+), n (%)	Population	Confirmation of diagnosis	Management of AS	Follow-up duration	No. of deaths
Treibel, 2016[10]	Prospective longitudinal, single center	146	6 (4%, 5.6% in calcific AS)	Severe AS undergoing SAVR	EMB (6), scintigraphy (DPD) (4)	SAVR (146)	2.3 (0.02-4.7) yrs	11 3 − ATTR(+) 8 − ATTR(−)
Galat, 2016[11]	Retrospective longitudinal, multicenter	16	16	Patients with concomitant ATTR and AS (severe AS 14, moderate AS 2)	EMB (6), scintigraphy (HMDP/DPD) (13)	SAVR (10), TAVR (2), conservative (4)	33 mos	7
Sperry, 2016[12]	Retrospective, longitudinal, single center	171	171	Group 1: patients with ATTR (144), Group 2: patients with ATTR + AS (27)	EMB or scintigraphy (PYP)	SAVR (11)	6 yrs	2 yrs mortality rate group 1: 37%; group 2: 33%
Longhi, 2016[13]	Cross-sectional, single center	43	5 (11.9%)	Severe AS + ≥1 of echocardiographic red flag for cardiac amyloidosis	EMB and scintigraphy (DPD) (5)	AV balloon angioplasty (5)	–	–
Cavalcante, 2017[14]	Retrospective, longitudinal, single center	113	9 (8%)	Severe and moderate AS scheduled for CMR	CMR-LGE	SAVR (42), TAVR (17)	18 (11-30) mos	40 (35%)
Castano, 2017[15]	Cross-sectional, single center	151	24 (16%)	Severe AS undergoing TAVR	Scintigraphy (PYP)	TAVR	2 yrs	–
Scully, 2018[16]	Prospective longitudinal, multicenter	101	14 (13.9%)	Severe AS undergoing TAVR	Scintigraphy (DPD)	TAVR	Data pending	Data pending

Values are represented as median or n (%). AS = aortic stenosis; ATTR = transthyretin cardiac amyloidosis; CMR = cardiovascular magnetic resonance; DPD = Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid; EMB = endomyocardial biopsy; HMDP=Tc-99m-hydroxymethylene diphosphonate; LGE = late gadolinium enhancement; PYP=Tc-99m-pyrophosphate; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

more pronounced ECG abnormalities than patients with solely AS. In a study by Castano et al,[15] patients with AS diagnosed with ATTR-CA compared to those with isolated AS had longer QRS duration (127 ms vs. 110 ms, p = 0.017) and higher prevalence of right bundle branch block (37.5% vs. 15.8%, p = 0.023). The most common arrhythmia in a reported series was atrial fibrillation, present in 41.7-67% of patients with concomitant AS and ATTR-CA [11,12,14,15] (Table 2). Although atrial fibrillation is a frequent comorbidity of the AS population, in patients with dual pathology, the prevalence of atrial arrhythmias was significantly higher: 67% in the ATTR-CA group vs. 20.2% in the isolated AS group, p = 0.006.[14] In summary, multiple ECG findings may suggest ATTR-CA but are nonspecific in isolation. Pseudoinfarct pattern, low ECG voltage, conduction abnormalities, and presence of atrial arrhythmias in a context of other compatible clinical signs should alert physicians to suspect cardiac amyloidosis.

3.2. Echocardiography

Echocardiography is the initial test in a pathway leading to the diagnosis of ATTR-CA. However, classical echocardiographic features such as left and right ventricular wall thickening, biatrial dilatation, mild pericardial effusion, thickening of atrioventricular valves and atrial septum, and restrictive filling pattern[1] may be absent at an early stage of the disease. Moreover, the absence of increased ventricular wall thickness does not exclude the disorder, as up to one-third of cases can present with normal LV wall size.[24] Increased myocardial echogenicity, termed “granular sparking,” strongly suggests cardiac amyloid, but it also becomes apparent at the late phase of the disease. It was traditionally believed that a concentric hypertrophic pattern is a classical feature of infiltrative cardiomyopathies, including cardiac amyloidosis. However, the data from the most recent echocardiographic and CMR studies[19,25] show that an asymmetric pattern does not exclude amyloid deposition, as asymmetrical septal hypertrophy was the most common morphologic phenotype, found in 79% of patients with ATTR-CA.[25]

LV wall thickening, impaired diastolic filling, and/or LV systolic dysfunction is frequently present in both pathologies. Nevertheless, these alterations appear to be expressed to a higher degree in patients with coexisting ATTR-CA. Patients with coexisting ATTR-CA and AS, in comparison to those with isolated AS, manifest greater LV wall thickness and higher LV mass index – mean wall thickness 18 mm ± 0.5 vs. 13 mm ± 0.3, mean LV mass index 105 g/m^2 ± 21 vs. 73 g/m^2 ± 21.[14] Diastolic dysfunction is another common finding in both of these entities, which progresses from a delayed relaxation pattern in the early stage through a pseudonormal pattern to a restrictive filling pattern in the late stage of the disease.[26,27] Patients with coexisting AS and ATTR-CA, compared to those with solely AS, exhibited more advanced grade of diastolic dysfunction – E/A ratio 2.3 vs. 0.9, p = 0.001; E wave deceleration time 176 ms vs. 257 ms, p < 0.0001).[15]

Low-flow low-gradient AS physiology should raise a suspicion for cardiac amyloid deposition, as it was frequently observed in reported series. Four studies have demonstrated that patients with AS and concomitant ATTR-CA, compared to those with isolated AS, had significantly lower LV ejection fraction, lower stroke volume index, and lower trans-aortic gradient.[11,13,14,15] In a study by Cavalcante et al,[14] out of 9 patients with AS diagnosed with ATTR-CA, 7 (78%) exhibited a low-flow low gradient pattern. Similarly, Galat et al[11] have found low-flow low-gradient AS physiology in 12 (86%) out of 14 patients with ATTR-CA. The observation of a low–flow low-gradient hemodynamic profile can serve as a red flag for cardiac amyloidosis and prompt search for other echocardiographic or clinical markers of the disease.

3.3. Deformation imaging

The analysis of myocardial deformation by tissue Doppler and speckle-tracking echocardiography plays an important role in the recognition of cardiac amyloidosis.[28] Reduction in LV longitudinal deformation is an early marker of cardiac amyloid deposition and may be detected even before LV wall thickening of heart failure occurs.[29–31] In a recent series, patients with concomitant ATTR-CA and AS exhibited significantly reduced LV longitudinal deformation measured by tissue Doppler or 2D speckle tracking.[10,11,15] In a study by Castano et al[15] patients with dual pathology compared to those with isolated AS had more impaired LV longitudinal deformation – global longitudinal strain −12% vs. −16%, respectively, p = 0.007; mitral annular tissue Doppler S′ 4.0 cm/s vs. 6.6 cm/s, respectively, p < 0.0001.[15] Furthermore, average mitral annular S′ was the best predictor of ATTR-CA in a multivariable logistic regression analysis, and a cut-off value of S' < 6 cm/s conferred 100% sensitivity to predict a positive 99mTc-PYP (99mTc-labeled pyrophosphate) amyloid scan. However, the relative apical sparing, with lower longitudinal deformation in basal segments with regard to apical ones, was not depicted in patients with ATTR-CA in that study. It has been speculated that the observed reduction in apical longitudinal strain in the ATTR group could be due to elevated wall stress and

Table 2
Clinical and imaging characteristics of patients with concomitant aortic stenosis and ATTR cardiac amyloidosis

First author, study year (Ref No.)	Age, years	Male, (%)	AF (%)	NYHA I/II/III/IV, (%)	IVST, mm	LVEF (%)	Mean AV gradient (mmHg)	LV SV index, ml/m^2	Low-flow low-gradient AS, %	GLS (%)	LV mass index, g/m^2	LGE (+) n (%)
Treibel, 2016[10]	77	67	–	–	16.7	67	–	–	–	12.6	121.7	2 (30%)
Galat, 2016[11]	79 ± 6	81	56	60 (III–IV)	18 ± 4	50 ± 13	33 ± 23	27 ± 7	86	7 ± 0.7		12 (100%)
Sperry, 2016[12]	79.4 ± 6.6	70.8	58.3	66.6 (III–IV)	18.6 ± 4.4	50 ± 13.9	21.8 ± 13	–	40.7	–	173.8 ± 55.3	–
Longhi, 2016[13]	84 (79–90)	80	–	100 (III–IV)	18 (16–21)	Reduced in 40%	–	–	80	–	–	–
Cavalcante, 2017[14]	88 ± 6	89	67	78 (III–IV)	18 ± 5	43 ± 17	30 ± 14	33 ± 10	78	–	105 ± 21	9 (100%)
Castano, 2017[15]	86.3 ± 5.7	91.7	41.7	0/25/75/0	13 ± 0.3	47.6 ± 17.6	35.2 ± 13.9	29.9 ± 10.5	37.5	12.4 ± 5.2	129.8 ± 43.6	–
Scully, 2018[16]	88 ± 6	50	–	–	–	–	37 ± 12	32 ± 7	–	–	–	–
Mean	83	75.6	55.8		17	51.5	31	30.5	64	10.7	136	

Values are represented as mean ± SD or n (%). AF = atrial fibrillation; AS = aortic stenosis; AV = aortic valve; GLS = global longitudinal strain; IVST = interventricular septal thickness; LGE(+) = late gadolinium enhancement positive; LVEF = left ventricular ejection fraction; LVSV = left ventricular stroke volume; NYHA= New York Heart Association.

increased afterload induced by AS that masks reduced apical deposition of amyloid in comparison to other segments. Therefore, the discriminatory value of 2D speckle-tracking in patients with dual pathology requires further investigation, as a classical apical-sparing pattern may be concealed by the presence of AS.

3.4. Cardiovascular magnetic resonance

CMR imaging has a high diagnostic value in cardiac amyloidosis and provides additive information through myocardial tissue characterization. LGE on CMR is very common in cardiac amyloidosis and represents interstitial expansion from amyloid deposition. The most frequent prototypical pattern is subendocardial and global transmural LGE, which is associated with the greatest interstitial amyloid deposition on myocardial histology.[25,32,33] Regional differences in LGE distribution have been described in patients with ATTR-CA, with higher involvement of basal segments and decreasing involvement extending to mid-cavity and apical levels.[33–35] CMR also enables more detailed evaluation of amyloid deposition in other parts of the heart. Right ventricular LGE is also extremely common and found in 37% to 97% of patients with ATTR-CA, depending on the stage of the disease.[36] Increased left atrial wall thickness and left atrial wall LGE were found in 70% and 90% of patients with ATTR, respectively.[37] (Fig. 1). There may be absence of late enhancement in cardiac amyloidosis, which should be taken into account, as amyloid deposition is a continuum from no LGE to subendocardial to transmural.[38] It appears that patients with biopsy-proven cardiac amyloidosis, but negative or minor LGE, have less advanced stage of the disease,[32] and restricting CMR protocols to LGE imaging carries the risk of missing early stages of cardiac amyloidosis.

Nonischemic patchy or mid-wall LGE is also found in approximately one-third of patients with severe AS and associated with impaired cardiac function and adverse clinical outcomes.[39] Therefore, patients with dual pathology may present with various combinations of CMR-LGE, creating difficulties in ATTR identification.

3.5. T1 mapping

Amyloid infiltration results in expansion of the extracellular space, which can be measured with T1 mapping, providing a novel tool to detect and quantify amyloid load. Elevated native myocardial T1 and extracellular volume (ECV) in cardiac ATTR was shown to be more sensitive than LGE imaging and had high diagnostic accuracy.[4,7,25] ECV was found to be elevated in patients with an early-stage disease when conventional clinical testing and LGE were normal.[4] Native T1 and ECV values become abnormal sequentially with increasing cardiac amyloid burden, being normal or mildly abnormal at an early stage and attaining the highest values at the advanced stage of the disease.[36,38] To date, only one study investigated native T1 and ECV values in patients with concomitant ATTR-CA and AS. The authors reported that, compared to patients with isolated AS, patients with concomitant ATTR-CA exhibited higher native T1 and ECV values: mean ECV 41.2% ± 16.7 vs. 27.9% ± 4.1, $p < 0.001$; mean native T1 1125 ms ± 49 vs. 1035 ms ± 60, $p = 0.002$.[14]

3.6. Nuclear imaging

Recent advances in nuclear imaging revolutionized ATTR-CA detection methodology. A new diagnostic algorithm was proposed and validated in 2016 that enabled noninvasive, non-histological diagnosis of ATTR amyloid deposition, diminishing the need for an endomyocardial biopsy. Three technetium-labeled radiotracers have been evaluated clinically for ATTR-CA identification: Tc-99m-pyrophosphate (PYP), Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and Tc-99m_hydroxymethylene diphosphonate (HMDP). It has been shown that grade 2 or 3 uptake on scintigraphy and the absence of a monoclonal protein have specificity and a positive predictive value of 100% for ATTR-CA.[40] Radionuclide bone scintigraphy has high sensitivity and may identify cardiac ATTR amyloid deposits early in the course of the disease, sometimes before the development of abnormalities on echocardiography or CMR.[41] Diagnosis of cardiac ATTR amyloidosis should be followed by TTR genotyping in all patients to differentiate between wild-type and mutant ATTR-CA. In the mutant ATTR-CA, the pathogenic mutation results in destabilization and misfolding of the transthyretin protein, whereas in the wild-type ATTR-CA, the genetic sequence of transthyretin is normal and the aging process is believed to be responsible for

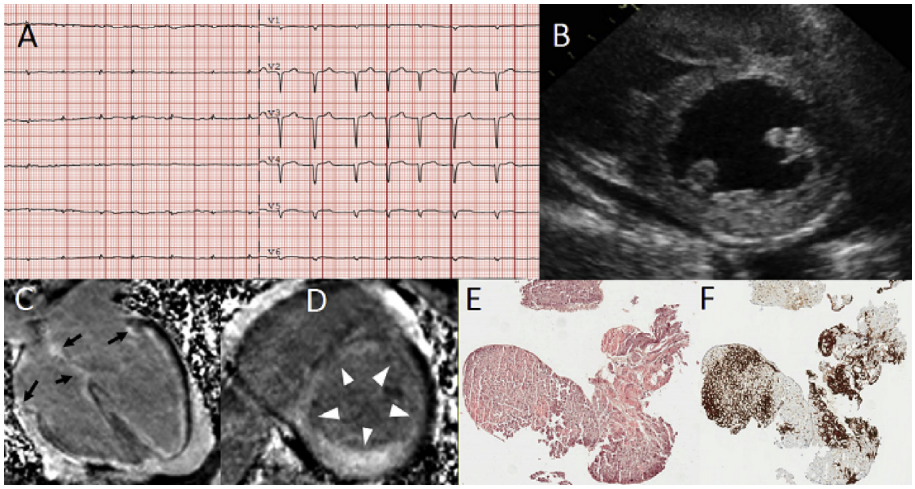

Figure 1. Multimodality imaging of a patient with advanced ATTR cardiac amyloidosis. (A) ECG showing atrial fibrillation, with a low-voltage, and pseudoinfarct pattern in precordial leads. (B) Echocardiographic parasternal short-axis view showing increased left ventricular wall thickness and mild pericardial effusion. Cardiac magnetic resonance imaging with global subendocardial circumferential enhancement of left ventricular walls in four-chamber (C) and short-axis views (arrowheads) (D). Note the diffuse enhancement of interatrial septum, both atria (arrows) and right ventricular wall. Endomyocardial biopsy with ATTR-related amyloid infiltration: (E) Congo red staining, (F) immunohistochemistry with anti-TTR antibodies.

protein instability and altered aggregation. Histological confirmation and typing of amyloid may still be required in patients undergoing a positive radionuclide scan and with the presence of a monoclonal protein.

3.7. Diagnostic workup of ATTR-CA in as

Given the high prevalence of calcific AS in the general population and the increasing frequency of TAVR in elderly patients, it is prudent to screen those in whom there is a suspicion of concomitant ATTR-CA. Echocardiography with deformation analysis may be the initial diagnostic steps, followed by contrast-enhanced CMR with T1 mapping. While endomyocardial biopsy with histological staining and tissue typing remain the gold standard for the diagnosis of ATTR-CA, it may not be appropriate in frail elderly patients. Nuclear imaging with technetium-labeled bone-seeking tracers, coupled with serum and urine electrophoresis for exclusion of monoclonal protein, may be a more suitable approach in this population (Fig. 2). However, owing to disease heterogeneity and the wide spectrum of clinical presentation, the optimal diagnostic algorithm for cardiac amyloidosis screening in patients with AS is still unclear and needs to be sorted out by further investigation.

4. Prognosis of patients with ATTR-CA and AS

The ATTR-CA is characterized by years of relative stability and slow disease progression. The reported median survival from diagnosis in untreated patients is approximately 3.6 years; however, a major determinant of outcomes is the extent of cardiac involvement.[42] In a recent meta-analysis of 23 studies, the predictors of death in patients with cardiac amyloidosis (AL and ATTR – wild and mutant types) were investigated.[43] Multivariate predictors of mortality were NYHA functional class, mean LV wall thickness, LV ejection fraction, and echocardiographic parameters of diastolic dysfunction (restrictive filling pattern, E/E' ratio, and E wave deceleration time). Right ventricular involvement, manifesting as increased right ventricular wall thickness and systolic dysfunction, is another independent predictor of poor prognosis in cardiac amyloidosis. It has been shown that right ventricular longitudinal systolic dysfunction, as assessed by depressed right ventricular longitudinal strain, is a negative prognostic marker in cardiac amyloidosis.[44]

To date, 3 longitudinal studies have investigated outcomes of patients with concomitant ATTR-CA and AS[10,13,14] (Table 1). In all of these studies, presence of ATTR-CA was associated with worse outcomes. In a study by Treibel et al,[10] 146 patients with severe AS

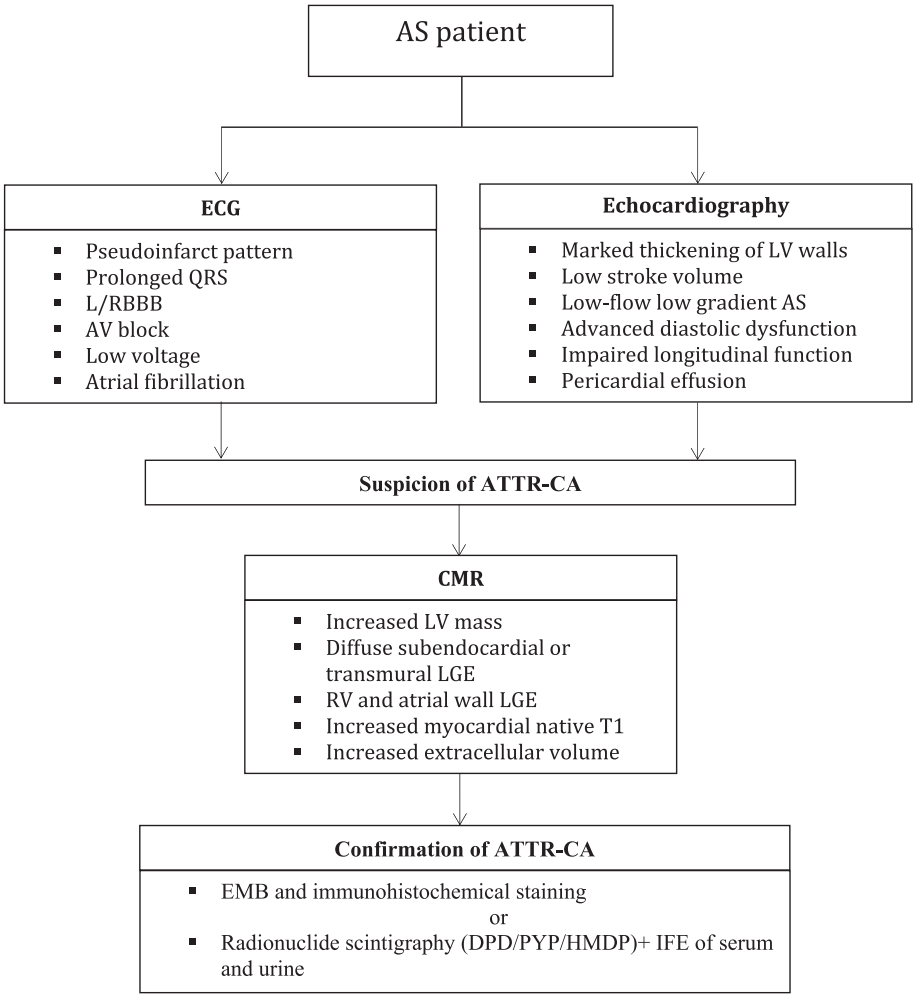

Figure 2. Flowchart of integrated imaging for the diagnosis of ATTR cardiac amyloidosis in aortic stenosis. AS = aortic stenosis; ATTR-CA = Transthyretin cardiac amyloidosis; CMR = cardiovascular magnetic resonance; DPD = Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid; EMB = endomyocardial biopsy; HMDP=Tc-99m-hydroxymethylene diphosphonate; IFE = immunofixation electrophoresis; LGE = late gadolinium enhancement; LV = left ventricular; PYP=Tc-99m-pyrophosphate; RV = right ventricular.

who underwent surgical AVR were followed up for a median of 2.3 years. Three out of 6 (50%) patients with AS who had ATTR-CA died, while 8 out of 106 (7.5%) deaths were observed in patients with isolated severe AS. Of all variables assessed, the presence of ATTR-CA had the highest hazard ratio for all-cause mortality (HR = 9.5, 95% CI 2.5-35.8, p = 0.001). In a retrospective study by Cavalcante et al,[14] patients with coexisting ATTR-CA had a higher 1-year all-cause mortality than patients with isolated AS (56% vs. 20%, p < 0.0001). Furthermore, patients with combined disease had higher all-cause mortality rate even after adjustment of possible confounders, including AVR, LV ejection fraction, and functional class. Sperry et al[12] in a retrospective study compared outcomes of ATTR-CA patients with and without AS. Study revealed no significant difference in the 2-year mortality rate between the two groups: 37% in the ATTR-CA with AS group and 33% in the isolated ATTR-CA group (HR = 1.22, 95% CI: 0.62-2.42, p = 0.566). These results suggest that the mortality in patients with combined disease may be driven by the presence of ATTR-CA, as patients with AS died at the same rate as those without AS despite some having undergone AVR. There is a need to further evaluate whether amyloidosis affects mortality synergistically with severe AS or whether it is the primary driver of poor outcomes in patients.

5. Management of patients with ATTR-CA and AS

Recognition of ATTR-CA is important before aortic valve intervention for better risk stratification and management choices, as unrecognized ATTR-CA in symptomatic patients with severe AS may be a cause of periprocedural complications in patients undergoing aortic valve intervention.[45] There are reports of perioperative mortality in ATTR-CA patients due to fatal arrhythmias, progressive heart failure, and myocardial infarction with mechanical complications.[46,47] On the other hand, TAVR, which is indicated for older and higher risk patients, is not without a risk as well. There are reports of LV rupture and complete atrioventricular block leading to death during or after the TAVR procedure in patients with cardiac amyloidosis.[48,49] Early diagnosis of ATTR-CA is also critical to gain the best efficacy of amyloid-directed therapies. Contemporary treatment strategies that stabilize transthyretin have recently reported to improve survival in patients with ATTR-CA.[50] Tafamidis treatment, compared to placebo, resulted in lower all-cause mortality, a 32% relative risk reduction in cardiovascular hospitalizations, and a lower rate of decline in the 6-minute walk test. The drug is currently under review by the U.S. Food and Drug Administration for ATTR-CA. The question regarding its use in patients with AS remains unanswered and will require dedicated prospective trials. There are no recommendations on the management of patients with concomitant AS and ATTR-CA, which makes the treatment of the coexisting diseases challenging for clinicians. Currently, management choices are left to the discretion of the treating heart team and should be discussed with each patient individually. The decision to operate should depend on the type of amyloidosis, the severity of the cardiac involvement, and the overall patient prognosis. Cardiac biomarkers can be used to risk stratify ATTR-CA patients. Two staging systems have been proposed. Thresholds of troponin T (0.05 ng/ml) and NT-proBNP (3.000 pg/ml) were used by The Mayo Clinic staging system.[42] The respective 4-year survival estimates were 57%, 42%, and 18% for stage I (both values below cutoff), stage II (one above), and stage III (both above), respectively. The staging system from the U.K. National Amyloidosis Center is applicable for both wild-type and mutant ATTR-CA and discriminates patients into three prognostic categories depending on their NT-proBNP levels and estimated glomerular filtration rate.[51] The risk and benefit of aortic valve intervention should be carefully reconsidered in patients at stage III cardiac amyloidosis. Keeping in mind the higher risk of periprocedural complications and reduced overall survival in patients with ATTR-CA, a more conservative approach may be adapted in this population. Medical management with repeated aortic valve balloon valvuloplasties could be preferred over valve replacement strategies. However, at present, there are no studies comparing different treatment strategies in patients with coexisting ATTR-CA and AS. Prospective multicenter studies in larger cohorts of patients with AS are needed before the conclusions could be drawn regarding the best management strategy. There is also lack of data whether aortic valve replacement will improve long-term survival in these patients. Outcome data are pending, but early results suggest higher medium-term mortality in patients referred for TAVR with severe AS (ATTRact-AS Study, NCT03029026). Our prospective multicenter study (NCT03585933) also aims at determining the prevalence, phenotype, and outcomes of ATTR-CA in patients with severe AS undergoing surgical and transcatheter AVR.

6. Conclusion

ATTR cardiac amyloidosis appears to be prevalent in AS, particularly among octogenarian males undergoing TAVR. Identification of cardiac amyloid deposition in the context of AS may be challenging because of overlapping clinical and imaging features. However, the presence of ATTR-CA is associated with a more severe AS phenotype, especially low-flow low-gradient AS. Preliminary data show that coexistence of ATTR-CA and AS is associated with worse outcomes, irrespective of the AS treatment received. Further work is pending to determine the optimal screening algorithm, AS management strategy, and to refine our understanding of the role of ATTR cardiac amyloidosis in these patients.

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Competing interests

The authors declare that they have no competing interests.

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